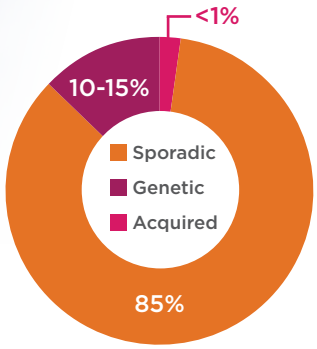
Prion Disease (PrD) Is a Rare, Progressive, Fatal, Neurodegenerative Disease[1,2]

PrD, also known as transmissible spongiform encephalopathies, describes a group of rare neurodegenerative diseases characterized by rapid, progressive neurological decline.[1,2]

PrD can occur via several etiologies (**Figure 1**)[1]:
- **Sporadic**, with no known exposure or genetic cause
- **Genetic**, due to variants in the prion protein gene (*PRNP*)
- **Acquired** from an exogenous source

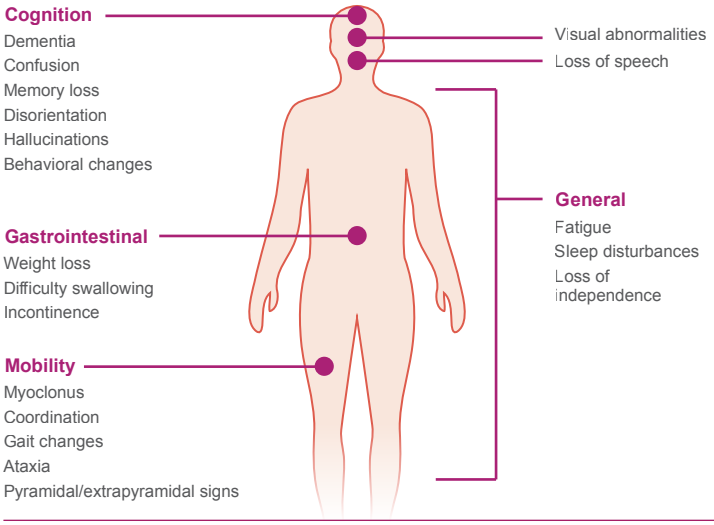
Misfolded prion protein scrapie (PrP^{Sc}) is the cause of disease in all types of PrD.[1]

Figure 1: Etiology of PrD[1]



PrD Is Typically Characterized by Rapidly Progressive and Nonspecific Cognitive, Motor, Cerebellar, and Visual Symptoms[3]

Figure 2: PrD Has a Range of Symptoms[3-6,a]



Types of PrD include[1]
- Creutzfeldt-Jakob disease (CJD)
- Fatal familial insomnia
- Gerstmann-Sträussler-Scheinker
- Variant CJD (vCJD)

Age of disease onset is unpredictable, but can be influenced by disease subtype. Onset generally occurs later in life (50-80 years of age). PrD has been diagnosed in people <20 and >80 years of age.[3,4,7,8]

Progressive neurological decline and death (**Figure 3**) is rapid and typically occurs within ~1 year of symptom onset, though some types of PrD have a longer duration.[2,7]

Disease progression can be assessed with the 20-point Medical Research Council Prion Disease Rating Scale (MRC-PDRS), which measures[4]:

- Cognitive function
- Speech
- Mobility
- Personal care/feeding
- Continence

Figure 3: Illustration of Disease Progression and Common Functional/Cognitive Milestones in PrD[4]

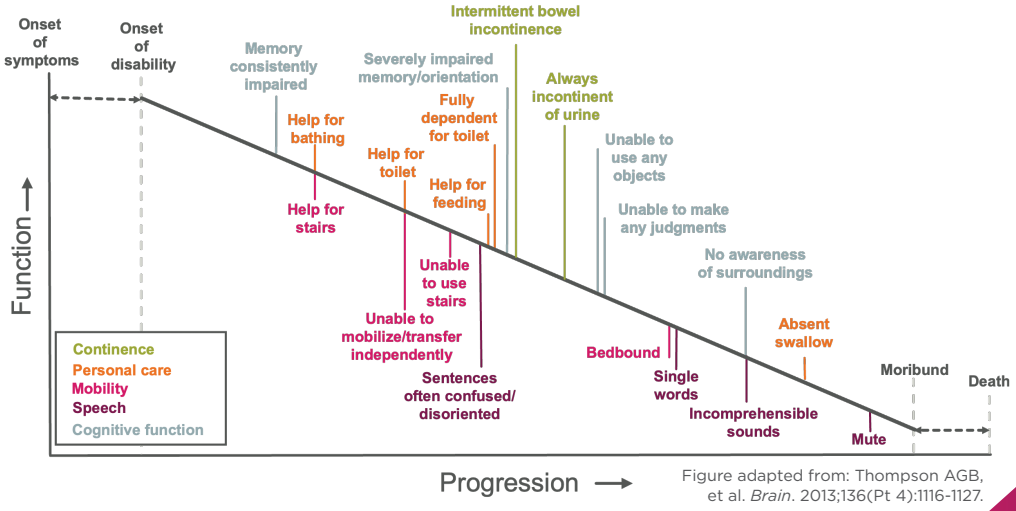


Figure adapted from: Thompson AGB, et al. *Brain*. 2013;136(Pt 4):1116-1127.

[a]Not a complete list of symptoms. Not all patients will experience all symptoms shown.

1. Altuna M, et al. *Medicina (Kaunas)*. 2022;58(4):473. 2. Bonda DJ, et al. *Neurosurg Focus*. 2016;41(1):E10. 3. Geschwind MD. *Continuum (Minneap Minn)*. 2015;21(6 Neuroinfectious Disease):1612-1638. 4. Thompson AGB, et al. *Brain*. 2013;136(Pt 4):1116-1127. 5. Appleby BS, Yobs DR. *Handb Clin Neurol*. 2018;153:399-408. 6. Ford L, et al. *Int Psychogeriatr*. 2019;31(8):1181-1190. 7. Sun Y, et al. *Clin Epidemiol*. 2020;12:1073-1081. 8. Chen C, et al. *PLoS One*. 2013;8(5):e62553.

Prompt Diagnosis and Treatments That Target the Underlying Pathophysiology Are Critical Unmet Needs for Patients With Prion Disease (PrD)[1-3]

up to 82% of patients are misdiagnosed on first assessment following symptom onset[3]

49% were previously diagnosed with cerebrovascular disease[4,a]

3.8 misdiagnoses on average before a PrD diagnosis is made[3]

Common Misdiagnoses[3-6,b]

- Viral encephalitis
- Depression
- Alzheimer's disease
- Dementia (non-specified)
- Paraneoplastic/ autoimmune disorders
- Peripheral vertigo
- Stroke
- Multiple sclerosis

PrD Diagnosis Is Based on Clinical, Imaging, and/or Laboratory Findings[7,8]

A high confidence probable diagnosis is based upon the following[7,8,c]:

Neuropsychiatric disorder PLUS positive RT-QuIC in CSF or other tissues OR:

- Rapidly progressive dementia with ≥2 of 4 key clinical features[d]
- And positive results in at least one laboratory test
  - Typical EEG (periodic sharp wave complexes) during an illness of any duration
  - 14-3-3 CSF assay (in patients with disease duration <2 years)
  - A high signal in caudate/putamen on MRI brain scan or ≥2 cortical regions either on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR)
- And without routine investigations indicating an alternative diagnosis[7]

Key clinical features that may raise suspicion for PrD and prompt timely and appropriate workup include[9,10]

1. **Rapidly progressive cognitive impairment**
2. Myoclonus
3. Visual or cerebellar signs
4. Pyramidal/extrapyramidal signs

Probable genetic PrD can be diagnosed based on the presence of a progressive neuropsychiatric disorder and either a pathogenic *PRNP* variant or definite or probable diagnosis of PrD in a first-degree relative.[9]

Treatment and Management Approaches Focus on Minimizing Symptoms and Maintaining Quality of Life[2]

Currently, there is no cure for patients with PrD that can stop, reverse, or address accumulation of PrP^{Sc}, the underlying pathogenic cause of disease.[1,2,11]

Disease management for PrD includes both pharmacologic and nonpharmacologic interventions that focus on managing symptoms and improving quality of life.[2]

[a]In a retrospective observational study of adults with CJD.[4] [b]Not a complete list. [c]Guidelines presented are from the CDC and ECDC and are specific for sporadic CJD.[7,8] [d]Four key clinical features include myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, akinetic mutism.[7,8]

CDC, Centers for Disease Control and Prevention; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; ECDC, European Centre for Disease Prevention and Control; EEG, electroencephalogram; *PRNP*, prion protein gene; PrP^{Sc}, scrapie; RT-QuIC, real-time quaking-induced conversion.

1. Shim KH, et al. *Prion*. 2022;16(1):265-294. 2. Appleby BS, Yobs DR. *Handb Clin Neurol*. 2018;153:399-408. 3. Paterson RW, et al. *Arch Neurol*. 2012;69(12):1578-1582. 4. Brown D, et al. Poster presented at: Prion 2023; October 16-20, 2023; Faro, Portugal. 5. Weeks K, et al. Poster presented at: 2023 Annual Meeting of the American Academy of Neurology; April 22-27, 2023; Boston, MA. 6. Day GS, et al. Poster presented at: 2023 Annual Meeting of the American Academy of Neurology; April 22-27, 2023; Boston, MA. 7. Centers for Disease Control and Prevention. Diagnostic criteria. Updated October 18, 2021. Accessed January 12, 2024. https://www.cdc.gov/prions/vcjd/diagnostic-criteria.html/ 8. European Centre for Disease Prevention and Control. EU case definition. Accessed January 12, 2024. https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/variant-creutzfeldt-jakob-disease/eu-case-definition/ 9. The National CJD Research & Surveillance Unit. Accessed February 1, 2024. https://www.cjd.ed.ac.uk/sites/default/files/diagnostic%20criteria.pdf/ 10. Mead S, Rudge P. *Pract Neurol*. 2017;17(2):113-121. 11. Altuna M, et al. *Medicina (Kaunas)*. 2022;58(4):473.